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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,709	07/12/2001	Karine Vidal	113308-002	4054

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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,709	VIDAL ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-22 and 24* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/04/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicant's amendment and arguments, filed on 06 April 2004, is acknowledged. Claims 18, 21-22,have been amended.

Status of Claims:

1b. Claims 19 and 23 have been cancelled. Claims 1-18, 20-22 and 24 are pending, of which claims 18, 20-22 and 24 are drawn to the elected invention and are under consideration.

Claims 1-17 stand withdrawn from consideration, as they are drawn to non-elected inventions.

Sequence compliance:

2. Applicants have submitted a computer readable form (CRF) and a paper copy of the sequence listing on 27 July 2004. The submitted CRF now complies with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Withdrawal of Previous Rejections:

3. The following previous objection is withdrawn in light of Applicants amendments filed on 06 April 2004:

3a. The rejection of claim 18, made under 35 U.S.C. 112, second paragraph for not reciting method steps is withdrawn, because claim 18 now recites said steps.

3b The rejection of claim 21 made under 35 U.S.C. 112, second paragraph for misspelling "glycosylation" is withdrawn, since said word is now correctly spelled.

Response to Applicants' arguments:

Claim rejections-35 USC § 112, first paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 18, 20-22, 24 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirements, for reasons of record set forth in the office action mailed on 30 May 2004, page 3-5.

Applicants argue that the claimed invention has been sufficiently described in the specification, because the specification details how the CD14 variant can be isolated from milk, and *N*-and *C*- terminal sequence analysis and optical biosenser assays have been performed for the CD14 variant recited in the instant claims. Applicants also argue that they have demonstrated that the mature milk soluble CD14 is biologically active by showing that incubation of *E. coli* in the presence of human serum or milk induces significant IL-8 levels. Furthermore, Applicants submit data demonstrating that sCD14 induces expression of sICAM-1, that TNF-α mRNA levels are decreased in rats fed rat milk substitute with sCD14, and that milk sCD14 in the presence of bacterial LPS induces the expression of ELAFIN and MCP-1 by intestinal epithelial cells induce. Thus Applicants conclude that they have demonstrated that human sCD14 can be effectively utilized to treat GI tract disorders. Applicants therefore, assert that the instant application satisfies the requirements under 35 U.S.C. 112, first paragraph.

These arguments have been fully considered but are deemed unpersuasive. Applicants fail to satisfy the written description provision of 35 U.S.C. 112, first paragraph, for the following reasons: although, the instant specification discloses that

amino acid sequence including *N* and *C* terminus of the mature milk derived CD14 is substantially identical to that of serum soluble CD14, and that the variant to be used in the instantly claimed method has only N-glycosylation and is about 48 kDa, none of these structural features are recited in the instant claims. Furthermore, the instant specification does not define the structure of a variant or a fragment of CD14 that shares at least 70% homology to the amino acid sequence of human serum CD14, to be used in the instantly claimed method. The skilled artisan would not be able to visualize the structure of a variant or a fragment of CD14 that is substantially identical or that has at least 70% identity to the serum soluble CD14, because there is no disclosure of the structure of said variant or fragment.

4b. Regarding the enablement requirement provision of 35 U.S.C. 112, first paragraph, instant application is enabling for a method of treating against intestinal bacterial infection by administering soluble CD14, and is non-enabling for a method of treating or preventing "all possible" GI tract disorders by administering an effective amount of a CD14 variant or fragment which retains the bioactivity of CD14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants demonstrate that human milk soluble CD14 induces ICAM-1, Elafin, MCP-1, and that said induction is blocked by the anti-CD14 monoclonal antibody, and that TNF-α mRNA levels are decreased in rats fed rat milk substitute with sCD14, however, they do not show that sCD14 treats and prevents "all possible" GI tract

diseases. Therefore, while soluble CD14 polypeptide might be useful against diseases that increasing ICAM-1, MCP-1, Elafin, or decreasing the levels of TNF-α are beneficial, the Applicants do not provide enough guidance to support that soluble CD14 can be used to treat or prevent "all possible" GI tract diseases. The specification lists "chronic hepatits" and "allergic reactions to food" as including GI disorders, however, as was set forth in the previous office action, Stelter et al showed that while sCD14 had protective effect against lethality of mice that were injected with LPS, it had no protective effect on LPS-induced *liver damage*, (see Stelter et al, page 206, bottom of column 1 and page 211, column 2). Although the specification asserts that infant formula with CD14 might be beneficial against food allergy, (page 20), Applicants have not shown that variant CD14 was used to treat "food allergic reaction".

Regarding, "prevention" recited in the claims, Applicants have not disclosed that they were able to determine in advance which patients were susceptible to a GI tract disorder, then administer sCD14, to prevent said patients from suffering any GI tract disorder.

Therefore, instant specification is only enabling for a method of treating against intestinal bacterial infection by administering soluble CD14.

Claim rejections-35 USC § 112, second paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5a. The rejection of claims 18, 20 and 24 made under 35 USC § 112, second paragraph, is maintained for reasons of record, set forth in the office action mailed on 30 May 2004, page7-8.

Applicants argue that support for " bioactivity of CD14", is found on page 2, lines 15-18. Applicants are correct in pointing out that the cited page recites some of the bioactivity of CD14, however, the metes and bounds of the claims are still unascertainable, because it is unclear which of these activities should said CD14 retain. Furthermore, art acknowledges that CD14 is also involved in apoptosis, therefore, it is unclear whether this activity is also a desirable activity for the recited CD14 variant or fragment to retain.

5b. Regarding the recitation of "GI tract disorders" in claim 18, the diseases recited on page 9, lines 15-22, are not the only disorders that affect the GI tract. GI tract includes the esophagus, stomach, small intestine, large intestine or colon, rectum, and anus, therefore, there are many more disorders that affect these areas, for example, cancer of the stomach or colon cancer or ulcer. Again the metes and bounds of which GI tract disorders are encompassed are not ascertainable. Reciting the specific disorders, will obviate this rejection.

5c. The rejection of claims 21 and 22, for reciting the phrase "includes" is maintained, because it is unclear whether the CD14 variant or fragment to be used in the claimed method is 70% homologous to serum CD14 that includes SEQ ID NO:1, with other components, if so what are these other components. Does it include all of SEQ ID NO:1 or parts of SEQ ID NO:1.

5d. Claim 22 recites "...0% homologous...", it is unclear whether this is a typographical error or whether the CD14 variant or fragment to be used in the claimed method has no homology to serum CD14.

Claim rejections-35 USC § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claim 18 stands rejected under 35 U.S.C § 102(b) as being anticipated by Haziot et al (1995), for reasons of record set forth in the office action mailed on 30 May 2004, page 10-11.

Applicants argue that the claimed invention is based upon the finding that mature milk includes an unknown variant of CD14, which has homology to the amino acid sequence of serum sCD14, but has a different mobility and is produced by mammary gland epithelial cell, has different glycosilation pattern with respect to the serum sCD14 and has a unique capacity for mediating bacterial interaction with intestinal surfaces. Applicants also argue that the primary focus of the cited art is that if recombinant soluble CD14 is injected into mice it purportedly reduces mortality due to LPS injection. Applicants submit that the capacity of sCD14 to bind to LPS and purportedly prevent the ultimate effects of sepsis as disclosed in Haziot et al reference, does not suggest that sCD14 can be utilized to effectively prevent or treat GI tract disorder, because sCD14 and LPS effectively act locally in the intestinal environment before crossing the intestinal barrier into systemic circulation. Applicants contend that Haziot et al only provide

evidence that CD14 in a soluble form may have benefits once injected into systemic circulation. However, the CD14 variant of the instant invention is orally administered to effectively act locally in the gastrointestinal tract to modulate responses to LPS, prevent disease and may prevent LPS passage into the blood circulation. Accordingly, Applicants argue that claim 18 is not anticipated by Haziot et al.

These arguments have been considered but are not deemed persuasive. Applicants are arguing limitations not recited in the claim, because although, the instant claim 18, recites "....administering to the patient an effective amount of a CD14 variant or fragment thereof.....", the claim does not recite the structural limitations argued by the applicant. It is unclear how the variant CD14 recited in claim 18 is distinguished from the sCD14 taught by Haziot et al. The instant claim 18 does not recite that the variant CD14 to be administered is from milk, that it has a different mobility and is produced by mammary gland epithelial cells, has different glycosylation pattern with respect to the serum sCD14. With respect to Applicants' argument that the variant CD14 used in the claimed method has the unique capacity for mediating bacterial interaction with intestinal surfaces, it is unclear whether *only* the variant CD14 used in the claimed method has this unique ability, or whether the mode of administration makes a difference. If the variant CD14 used in the claimed method is the only CD14 that has this unique capacity, then Applicant must explain what distinguishes this variant from other CD14 polypeptides. With respect to Applicants' argument that the CD14 variant used in the instant method is administered orally, the claimed method does not recite "oral administration", therefore, again Applicants are arguing limitations not recited in

the claim. Claim 18 encompasses a method of administering a variant of CD14, and Haziot et al reference discloses a method of injecting human recombinant soluble CD14(rsCD14), into a mammal. The claimed process is not directed to a new use, it is the same use and it consists of the same method as described by Hiziot et al. Therefore, Haziot et al reference anticipates instant claim 18.

New Rejections:

Claim rejections-35 USC § 102(b):

7. Claims 18, 20-22 and 24 are rejected under 35 U.S.C § 102(b) as being anticipated by Julius et al (1998).

7a. Julius et al disclose a method of administering infant formula that has been incorporated with CD14 to an infant, (see page 4, lines 11-14). Julius et al disclose that colsotrum and breast milk taken four days post-partum contained roughly 20 fold higher concentration of CD14 than did normal serum and that milk taken 78 days post-partum contained around 3-5 fold higher CD14 than normal serum (see bottom of page 27 and top of page 28). Julius et al teach that the use of CD14 as an infant formula additive may benefit the neonate, by stimulating its immune system, (page 28, lines 15-21).

Julius et al also disclose a CD14 polypeptide that shares 100% homology to SEQ ID NO:1 recited in claims 21 and 22.

Instant claims 18, 21-22 and 24 are drawn to a method of administering a variant of CD14 or fragment thereof into a patient to treat GI tract disorder, said CD14 being in an infant formula, and claims 21 and 22 further limit the invention the use of a CD14 that

shares 70% homology to the SEQ ID NO:1, while claim 24 adds the limitation of administering to "an infant".'

The Julius et al reference meets all the limitations recited in instant claims 18, 22-22 and 24.

Claim rejections-35 USC § 112, first paragraph:

8a. Claim 18 recites ".....in a *patient* which comprises the step of administering to the *patient* an effective .....", however, this recitation introduces new matter into the claim, because, the word "*patient*", does not seem to appear anywhere in the instant specification, and the Applicants have not pointed where support for the amendment to claim 18 is found in the specification.

Thus, the limitation ".....*patient*...", recited in claim 18, does not meet the written description provision of 35 U.S.C. 112, first paragraph, because it was never recited in the specification, as such this introduces new matter into the claim.

Conclusion:

9. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
15 October 2004

JANET ANDRES
PRIMARY EXAMINER